UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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SEP - 8 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Sumithrin (d-phenothrin) - Review of Background Hepatocellular Tumor Incidence Data For The B6C3F1 Mouse In Support Of FAP #8H5559 and EPA Registration No. 10308-6

HED Project No.: 9-1393
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Hepatocellular tumor historical control data for the B6C3F1 mouse have been submitted in response to the Agency's request for further clarification of the sumithrin mouse combined chronic feeding/oncogenicity study (LSR Report No. 86/SUM007/166, April 1987, Sumitomo Reference No. ET-71-0109; EPA MRID No. 402764-02). The Agency review[1] classified this study as Core Supplementary and subsequently discussed their concern with regard to "the spontaneously occurring early [liver] tumors (20% at 53 weeks) and the incidence of [liver] tumors at termination of the study (50% at 104 weeks)" observed in the male control group. In addition, other issues were identified which complicate the interpretation of the liver tumor data. These issues pertain to

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[1]Memo, E.Budd to J.Tavano, March 16, 1989. Sumithrin (d-phenothrin) - Review of Toxicity Studies Submitted by Sumitomo Chemical Company Ir. Support of FAP #1H5283 and EPA Registration No. 10308-6.

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questions concerning the selection of dose levels, particularly with regard to a maximum tolerated dose as well as the fact that sumithrin is a synthetic pyrethroid compound, a class of chemicals which has been associated with liver tumors in mice.

The registrant has submitted historical control data for liver neoplasms (adenoma and carcinoma) for 13 studies conducted from 1979 to 1984, lasting from 104 to 117 weeks and using the B6C3F1 mouse. Of the 13 submitted studies, seven studies were conducted at an unnamed laboratory(s) within the United States and the remaining six studies were performed at an unnamed laboratory(s) in the United Kingdom. It should be reemphasized that in assessing the toxicological significance of historical control information, it is best to use data generated from the same laboratory and supplier, under the same conditions and within a five to ten year time of the study in question. Therefore, since the sumithrin combined chronic feeding/oncogenicity study was conducted in Essex, England and completed in 1987, the six studies performed in the "United Kingdom" from 1982 to 1984 were considered the most appropriate data set to be analyzed. These data are summarized below for male (Table 1) and female (Table 2) animals.

Table 1. Liver Neoplasm Historical Control Data[1] - Males

Study #	9	10	12	13	15	19	SUM[3]
Date	1982	1983	1983	1983	1983	1984	1987
# Examined	52	52	52	52	52	52	50
Adenoma[2]	11(21%)	11(21%)	21(40%)	13(25%)	6(12%)	7(13%)	11(22%)
Carcinoma	11(21%)	14(27%)	5(10%)	2(4%)	9(17%)	7(13%)	14(28%)
TOTAL	22(42%)	25(48%)	26(50%)	15(29%)	15(29%)	14(26%)	25(50%)

[1]United Kingdom laboratory only, 104 weeks duration
[2]Excluding animals bearing carcinoma.
[3]Sumithrin combined chronic feeding/oncogenicity (LSR #86/SUM007/166; April 1987), 104 weeks duration.

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Table 2. Liver Neoplasm Historical Control Data[1] - Females

Study #	9	10	12	13	15	19	SUM[3]
Date	1982	1983	1983	1983	1983	1984	1987
# Examined	52	52	52	52	52	52	50
Adenoma[2]	1(2%)	5(10%)	11(22%)	1(2%)	6(12%)	5(10%)	3(6%)
Carcinoma	2(4%)	0(0%)	5(10%)	0(0%)	3(6%)	1(2%)	4(8%)
TOTAL	3(6%)	5(10%)	16(32%)	1(2%)	9(18%)	6(12%)	7(14%)

[1]United Kingdom laboratory only, 104 weeks duration
[2]Excluding animals bearing carcinoma.
[3]Sumithrin combined chronic feeding/oncogenicity (LSR #86/SUM007/166; April 1987)

These data indicate that the spontaneous response seen in the sumithrin combined feeding/onco study are within, although on the high side, of the range observed in historical controls. However, the high incidence of hepatocellular tumors observed in the male control animals treated with sumithrin continue to raise concerns regarding the oncogenic potential of the compound at higher lifetime doses.

Comparison of incidence data for historical controls and the sumithrin study are summarized for males (Table 3) and females (Table 4) below.

Table 3. Male B6C3F1 Mice

Lesion	Adenoma	Carcinoma	Combined Total
-HC[1]	69/312 (22%)	48/312 (15%)	117/312 (38%)
-HC Range	12-40%	4-27%	26-50%
-Sumithrin[2]			
-Control	11/50 (22%)	14/50 (28%)	25/50 (50%)
- 300 ppm	14/50 (28%)	15/50 (30%)	29/50 (60%)
-1000 ppm	18/50 (36%)	15/50 (30%)	33/50 (66%)
-3000 ppm	15/50 (30%)	15/50 (30%)	30/50 (60%)

[1]Historical control data average for six studies.
[2]Combined chronic feeding/oncogenicity (LSR #86/SUM007/166; April 1987); numbers taken from memo, Budd to Tavano, 3-16-89.

Table 4. Female B6C3F1 Mice

Lesion	Adenoma	Carcinoma	Combined Total
-HC[1]	29/312 (9%)	11/312 (4%)	40/312 (13%)
-HC Range	2-22%	0-10%	2-32%
-Sumithrin2			
-Control	3/50 (6%)	4/50 (8%)	7/50 (14%)
- 300 ppm	5/50 (10%)	7/50 (14%)	12/50 (24%)
-1000 ppm	7/50 (14%)	6/50 (12%)	13/50 (26%)
-3000 ppm	6/50 (12%)	9/50 (18%)	15/50 (30%)

[1]Historical control data average for six studies.
[2]Combined chronic feeding/oncogenicity (LSR #86/SUM007/166; April 1987); numbers taken from memo, Budd to Tavano, 3-16-89.

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Background data

Neoplastic pathology for male B6C3F1 mice

Code (BCM)	1	2	3	5	6	7	8	9	10	12	13	15	19
Commenced	1979	1979	1980	1980	1981	1981	1982	1982	1983	1983	1983	1983	1984
Source	USA	USA	USA	USA	USA	USA	USA	UK	UK	UK	UK	UK	UK
Housing	4	4	4	4	4	4	4	4	4	4	4	4	4
Study duration (Weeks)	107	107	117	104	104	104	104	104	104	104	104	104	104
Tissue and neoplasm													
Liver													
No. of mice examined	59	59	104	60	104	52	52	52	52	52	52	52	52
Hepatocellular adenoma	13(22%)	6(10%)	11(11%)	8(13%)	32(31%)	19(37%)	14(27%)	12(23%)	14(27%)	21(40%)	13(25%)	6(12%)	7(13%)
Hepatocellular carcinoma	14(24%)	8(14%)	23(22%)	7(12%)	19(18%)	12(23%)	8(15%)	11(21%)	14(27%)	5(10%)	2(4%)	9(17%)	7(13%)
Hepatocellular adenoma+	13(22%)	6(10%)	11(11%)	8(13%)	32(31%)	16(31%)	13(25%)	11(21%)	11(21%)	21(40%)	13(25%)	6(12%)	7(13%)
Hepatocellular adenoma/ carcinoma	27(46%)	14(24%)	34(33%)	15(25%)	51(49%)	28(54%)	21(40%)	22(42%)	25(48%)	26(50%)	15(29%)	15(29%)	14(27%)

+ Excluding animals bearing carcinoma

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Attachment 2

Background data

Neoplastic pathology for female B6C3F1 mice

Code (BCM) :	1	2	3	5	6	7	8	9	10	12	13	15	19
Commenced :	1979	1979	1980	1980	1981	1981	1982	1982	1983	1983	1983	1983	1984
Source :	USA	USA	USA	USA	USA	USA	USA	UK	UK	UK	UK	UK	UK
Housing :	4	4	4	4	4	4	4	4	4	4	4	4	4
Study duration (Weeks) :	85	98	115	104	104	104	104	104	104	104	104	104	104
Tissue and neoplasm													
Liver													
No. of mice examined :	60	59	104	60	104	52	52	52	52	50	52	52	52
Hepatocellular adenoma :	2(3%)	5(8%)	11(11%)	6(10%)	13(13%)	10(19%)	4(8%)	1(2%)	5(10%)	11(22%)	1(2%)	6(12%)	5(10%)
Hepatocellular carcinoma :	0(0%)	1(2%)	4(4%)	3(5%)	6(6%)	4(8%)	0(0%)	2(4%)	0(0%)	5(10%)	0(0%)	3(6%)	1(2%)
Hepatocellular adenoma+ :	2(3%)	5(8%)	11(11%)	6(10%)	13(13%)	9(17%)	4(8%)	1(2%)	5(10%)	11(22%)	1(2%)	6(12%)	5(10%)
Hepatocellular adenoma/ carcinoma :	2(3%)	6(10%)	15(14%)	9(15%)	19(18%)	13(25%)	4(8%)	3(6%)	5(10%)	16(32%)	1(2%)	9(17%)	6(12%)

+ Excluding animals bearing carcinoma

Attachment C